Polyneuropathy

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SUMMARY

Polyneuropathy is characterized by simultaneous bilateral symmetrical involvement of peripheral nerves. Clinical features in fully-developed cases are paresthesias, irregular 'glove and stocking' cutaneous sensory loss, loss of deep sensations, weakness of distal muscles of extremities, and absent deep tendon reflexes. The most common forms of neuropathy encountered in practice are – alcohol-induced, Guillain-Barre syndrome, and that secondary to diabetes mellitus. Since PN has many causes, a scheme based on clinical features is presented so that the possibilities can be narrowed and pursued with further investigations.

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THE TERM 'polyneuropathy' (PN) implies multiple bilateral symmetrical synchronous affection of peripheral nerves, producing varying degree of sensory, motor, and autonomic function impairment. The involvement is usually seen in all four extremities.

Anatomy, Histology and Pathology

Spinal peripheral nerve is made of three components – sensory, motor and autonomic. It is formed by the union of sensory and motor roots distal to the spinal ganglion, with the sympathetic fibers joining more distally. Nerve fibers have a fine diameter (1-16 microns) and an extraordinary length up to one meter. They are of two types:

1. Myelinated: the axon is covered by thick myelin sheath which is divided in longitudinal segments by nodes of Ranvier. The length of segment varies with thickness of nerve fiber and each segment is covered by a Schwann cell.

2. Non-myelinated: no discernible node of Ranvier. The nerve fibers over two micron diameter are usually myelinated, while smaller ones are non-myelinated. Figure 1 shows the parts of a peripheral nerve.

Peripheral nerves are comparable to cables which transmit information between the centre (central nervous system) and periphery (body). The messages (impulses) travel at different rates in different nerves and in different fibers of the same nerve. The conduction is rapid in thick myelinated fibers and slow in the non-myelinated fibers. Myelin sheath serves as electrical insulator, the current entering and leaving only at the node of Ranvier (saltatory conduction). For metabolic needs, the axon depends on the neuron of origin and myelin sheath on the Schwann cell. Nerve fibers and the myelin sheath have elaborate enzyme systems requiring active metabolism. These may be disturbed during infection, toxicity, or metabolic disorders.

The pathological process of PN involves peripheral nerves diffusely and symmetrically. Regardless of the cause, when the nerves are involved in this fashion, the neurons which innervate the most distal portions suffer the most; hence the term 'peripheral neuropathy'. Sensory, motor, or autonomic fibers of the peripheral nerve may be perfunctorily affected by different etiologic agents and the severity of deficit may be different depending on the cause.

This selectivity provides a valuable clue to the cause of polyneuropathy. Pathological lesions may primarily affect axons, myelin sheath, interstitial tissue, or all nerve components. The major causes of diffuse peripheral nerve lesions are metabolic or toxic. The term 'neuritis', formerly frequently used, is now reserved for cases where inflammation is the major pathology. Since this is an uncommon lesion, the term 'polyneuropathy' is often used for all diffuse peripheral nerve involvements. When the disease process involves the nerve roots diffusely, the term 'polyradiculopathy' is used. Involvement of this site is often seen with previous infection or allergy.

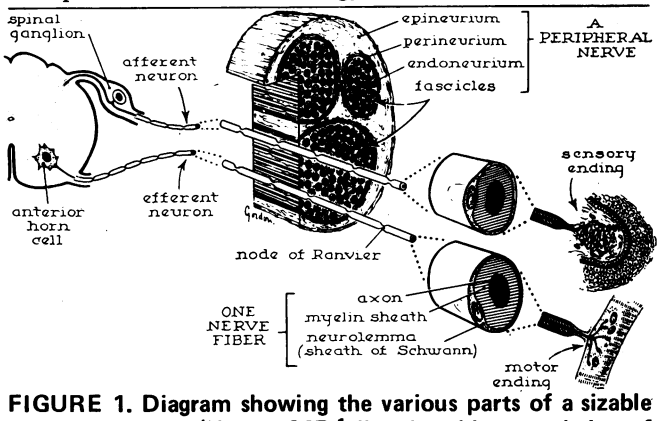

FIGURE 1. Diagram showing the various parts of a sizable peripheral nerve. (Ham, 1965.[1] Reprinted by permission of the publisher, J. B. Lippincott Co., Philadelphia.)

Peripheral neuropathy affects all ages but is most common in young or middle-aged adults. Symptoms usually begin synchronously and symmetrically in distal parts of lower extremities, subsequently involving upper extremities in the same fashion. Most cases have both sensory and motor deficit. The initial symptom is often numbness, prickling, burning, hypersensitivity to cold, hyperpathia, or dulling of touch sensation. Occasionally, pain may be a feature – usually mild, but rarely burning or sharp. In some sensory neuropathies the patient may have no discomfort in spite of objective sensory impairment evidence, e.g. difficulty walking in the dark, or unrecognized burns. There is impairment of all sensory modalities in distal parts of the extremities. Loss of vibratory sense is often earliest and most pronounced. Cutaneous sensory impairment in fully developed cases may be of irregular 'glove and stocking' distribution. Sensory impairment is usually more marked in lower than upper extremities.

Symptoms of motor weakness depend on rapidity of onset and severity of involvement. Motor weakness of sudden onset is always reported, while slowly progressive weakness may often go unrecognized. Muscle pain and tenderness are often seen in acute motor weakness. Flaccid weakness of distal parts, more marked in the legs than in the arms, is the usual picture. Deep tendon reflexes (DTR) are absent or hypoactive in all cases. Autonomic dysfunction in polyneuropathy may manifest as trophic skin changes, nocturnal diarrhea, incontinence or retention of urine, impotence, or postural hypotension.

Peripheral neuropathy may be mild (only subjective symptoms of paresthesias), moderate (subjective symptoms and mild motor, sensory, and reflex changes) or severe (paralysis, profound sensory deficit, absent DTR and autonomic dysfunction).

Diagnosis and Differential Diagnosis

Diagnosis in fully-developed neuropathy is easily established from history and examination alone. In mild cases or those with predominant sensory or motor involvement, further laboratory tests may be required. The most valuable tests to establish the diagnosis are electrical stimulation of peripheral nerves to determine conduction velocity (CV) and electromyography. Slowing of CV is the most common laboratory abnormality. Figures 2-6 show comparison of motor and sensory conduction in different nerves of a patient with polyneuropathy (B) to a normal age-matched control (A). In B, there is marked slowing of motor conduction in comparable segments of each median and peroneal nerves. Distal latency is also prolonged. Sensory conduction shows slowing and reduction in amplitude of sensory action protenial. These tests indicate diffuse sensory and motor dysfunction of peripheral nerves, i.e. polyneuropathy. When axonal damage is present, an electromyogram will show fibrillation potentials which are diagnostic of lower motor neuron lesions, but not of peripheral neuropathy as such.

Protein elevation of 45-75 mg percent in CSF is common in most neuropathies, but higher values are seen in diabetic PN and Guillain Barre syndrome. Histological examination of the affected muscle helps differentiate neurogenic from myopathic illness. Figure 7 is an example of neurogenic atrophy showing clusters of atrophied muscle fibers scattered among other groups of healthy fibers.

The following conditions which resemble PN can be differentiated by their features:[2-5]

1. Mononeuritis multiplex: multiple nerve trunk involvement. Asymmetrical. Asynchronous. Acute onset over hours – pain, paresthesia, and weakness in distribution of nerve. Days or weeks later, distant nerve involvement.
2. Motor neuron disease: no sensory findings. Often upper and lower motor neuron involvement. Normal or near normal CV.
3. Poliomyelitis: acute febrile illness. No sensory deficit. Asymmetrical. Elevation of proteins and cells in CSF. Normal or near normal CV.
4. Tabes dorsalis: history of syphilis. Tabetic crisis. Argyll Robertson pupils. Positive Wassermann in CSF, Normal CV.
5. Spinal cord tumor: radicular pain. Corticospinal tract involvement. May be segmental sensory level. Myelogram helpful.
6. Multiple sclerosis: disseminated lesions in CNS. Remissions and exacerbations. DTR often brisk. Normal CV and EMG.
7. Subacute combined degeneration: upper motor neuron involvement. Abnormal vitamin B12 absorption.

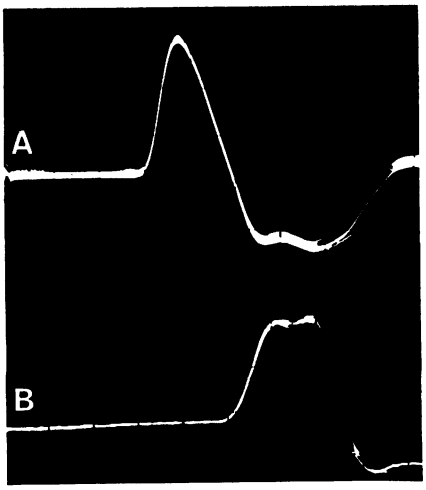

Figure 2. A. Left median nerve: motor conduction between elbow and thenar eminence in normal control (conduction velocity 65.7 meters/second). B. Same nerve in patient with polyneuropathy. (Conduction velocity 42.8 meters/second).

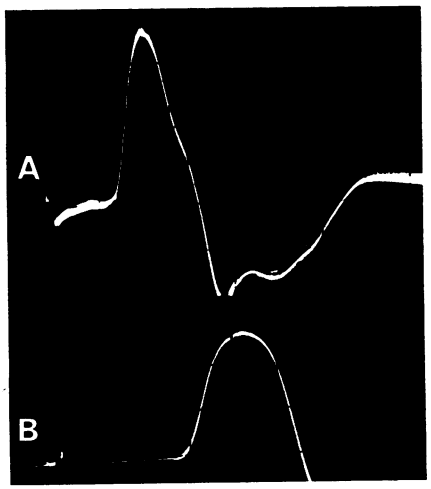

Figure 3. A. Left median nerve motor conduction from above the wrist to thenar eminence in normal control. (Distal latency 2.8 milliseconds). B. Same nerve in patient with PN. (Distal latency 5.4 m.s.).

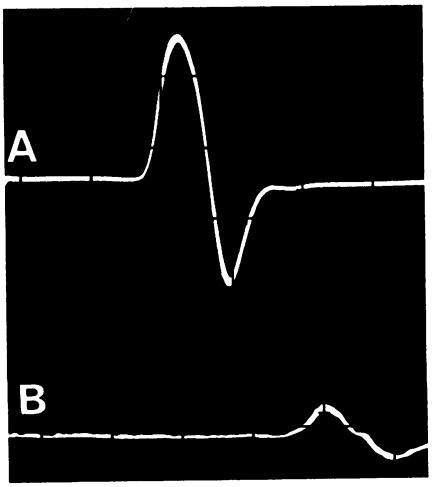

Figure 4. A. Left peroneal nerve motor conduction between knee and dorsum of foot in normal control. (Conduction velocity 56.6 m/s). B. Same nerve in patient with PN. (Conduction velocity 39.0 m/s).

8. Syringomyelia: dissociated (temperature and pain), sensory loss in involved (cervical) segment. Myelogram helpful.

9. Frontal parasagittal meningioma: spastic weakness. DTR hyperactive.

10. Progressive muscular dystrophy: often inherited. Selective muscle involvement. Predominant proximal. No sensory deficit. Normal CV.

11. Polymyositis and dermatomyositis: proximal muscle weakness. Pharynx and anterior neck muscle involvement. No sensory deficit. Elevated creatine phosphokinase. Normal CV.

12. Metabolic myopathies (e.g. thyrotoxic): proximal involvement. No sensory deficit. Features of basic disease. Normal CV.

13. Hypokalemic periodic paralysis: early morning flaccid paralysis. No sensory deficit. Complete recovery within hours.

14. Restless leg syndrome: creeping sensation in legs at rest, relieved on movement. No objective sensory, motor, or reflex changes. Normal CV and EMG.

15. Hysteria: sensory loss without anatomical borders. Weakness incongruent with functional deficit. Normal DTR. Normal CV and EMG.

The course of polyneuropathy varies from complete recovery within a few weeks to progressive fatal outcome. Prognosis depends on the cause, the stage of disease when treatment commenced, and complications.

There are perhaps more known causes of polyneuropathy than for any other clinical syndrome. Well over 100 agents or illnesses are known to produce PN and the list is continuously growing. The major challenge is to establish the cause of this disease. Pathological classification, though adequate, often does not help a physician taking care of the patient. Determination of cause and effect relationship in polyneuropathy depends on establishment of a concurrent condition which is known to cause PN. Even with the most exhaustive studies, the cause is not recognized in many cases. To avoid a wild goose chase for the etiology, the following scheme is proposed.

Three aspects of PN should be evaluated in each case:
Involvement of Components.

Although most polyneuropathies have both sensory and motor components, predominance of one component is fairly common. Predominant sensory involvement is seen when the PN is caused by:

1. Alcohol – vitamin deficiency.
2. Metabolic amyloidosis, diabetes mellitus, uremia, malabsorption and vitamin B deficiency states.
3. Poisoning – arsenic.
4. Malignancy (mainly lung).
5. Infection – leprosy.
6. Drug-induced – isoniazid.
7. Systemic illness such as collagen diseases or multiple myeloma.

Predominant motor neuropathy is seen when the PN is:

1. Post or para-infectious – Guillain Barre Syndrome, post-diphtheric neuropathy, and neuropathy associated with infectious mononucleosis.
2. Metabolic – porphyria.
3. Seratogenic or post-vaccination polyneuropathy.
4. Heavy metal toxicity – lead.
5. Hereditary neuropathies – Charcot-Marie-Tooth disease, Dejerine-Sottas disease, and Refsum's disease.
6. Drug-induced – vincristine neuropathy.

Rare pure forms of sensory neuropathies include:

1. Hereditary sensory radiculoneuropathy.
2. Congenital sensory neuropathy.
3. Riley-Day syndrome.
4. Dorsal root ganglion involvement associated with malignancy.
5. Friedreich's ataxia.

Onset.

Sudden onset, i.e. within hours or days, is seen in postinfectious such as Guillain-Barre syndrome, porphyria, and some cases of alcohol-vitamin B deficiencies. Gradual onset, i.e. weeks or months, is the most common mode of presentation in polyneuropathies. This is true of metabolic neuropathies such as diabetic, toxic (lead), infectious (leprosy), and deficiency neuropathies.

Imperceptible onset occurs when the patient does not realize the deficit. It may go unnoticed for months or even years and may be discovered accidentally. The group of diseases presenting like this are mostly hereditary neuropathies such as Charcot-Marie-Tooth disease, Refsum's disease, Dejerine-Sottas disease, hereditary sensory neuro-

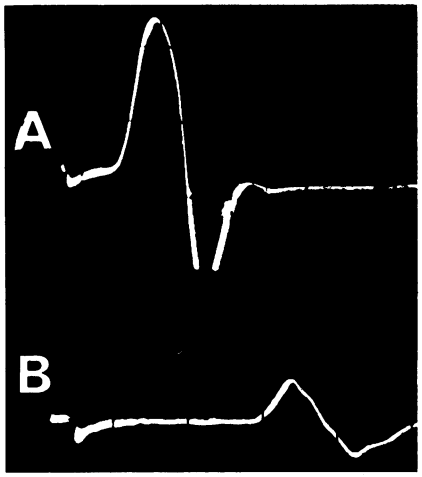

Figure 5. A. Left peroneal nerve motor conduction above ankle and dorsum of foot in normal control. (Distal latency 3.4 m/s). B. Same nerve in patient with PN. (Distal latency 12 m/s).

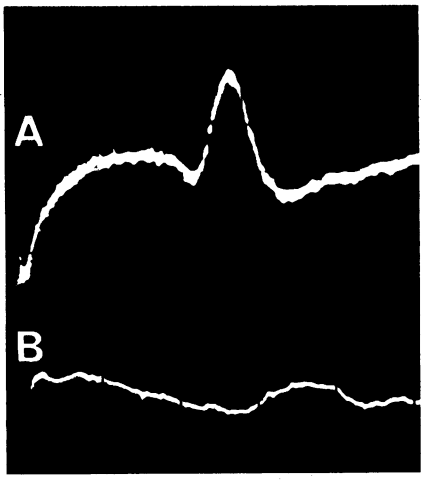

Figure 6. A. Sensory conduction in left median nerve between left index finger and above wrist in normal control. (Sensory latency 2.5 m/s). B. Same nerve in patient with PN. Sensory latency 3.3 m/s).

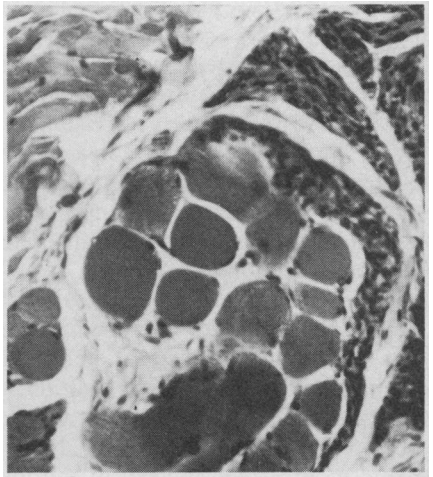

Figure 7. Transverse section of neurogenic muscle atrophy (H & E X 220). One cluster of normal muscle fibers surrounded by several clusters of smaller atrophied fibers.

pathies, as well as some congenital neuropathies.

Distribution.

In most polyneuropathies, major involvement is in the distal parts of the extremities. In Guillain-Barre syndrome, PN with infectious mononucleosis in porphyric PN, proximal involvement may be the dominant feature.

In all cases of polyneuropathy, the history should establish whether the patient is suffering from diabetes, malignancy, lymphoma, uremia, vitamin deficiency, amyloidosis, porphyria, collagen disease, exposure to toxins, arsenic poisoning, or alcohol ingestion, and whether there is a family history of PN. The preference for lab tests is established after evaluation and narrowing the list of possibilities as mentioned above. Where that is not possible, glucose tolerance test, blood urea and creatine level, Schilling test, urine for porphobilinogen, liver function test, plasma electrophoresis, and heterophile antibody estimation are generally useful screening procedures in neuropathies.

Examination of CSF is valuable in post-infectious PN. Nerve biopsy will be helpful in establishing the diagnosis of hereditary neuropathies and some rare forms.

Alcohol-Vitamin Deficiency Polyneuropathy

The patient is addicted to a large amount of alcohol. Approximately 1-1.5 litres of wine per day for eight to ten years will result in PN. The exact cause of PN is still disputed, but most workers believe inadequate diet (protein and vitamin B) is responsible, even when caloric intake is adequate. Direct toxic effect of alcohol may play a role.

The common age of onset is between 40 and 70. Onset is mostly gradual, over weeks or months, though occasionally it may be rapid. PN begins as paresthesia – a burning, prickly, or jabbing sensation, worse in the feet than in the hands. The symptoms are worse when walking or standing. Sensory symptoms are followed by motor weakness characterized by foot drop. Unless the condition is treated early, similar symptoms will appear in the upper extremities. Sensory loss of irregular 'stocking and glove' type is seen in fully developed cases. Calf muscles are usually tender. Weakness is most marked in the distal parts, i.e. feet and hands, and more prominent in extensor than in flexor muscles. The DTR are absent or hypoactive. The nerve CV are slow.

Diagnosis is based on history of alcoholic intake and presence of other features of chronic alcoholism, e.g. portal cirrhosis and Wernicke's encephalopathy, etc. The course of PN is progressive if not treated. With treatment, the recovery is usually slow. This is especially true if the treatment is started after motor deficit is established. In uncomplicated cases the mortality rate is low. When other CNS complications are present (e.g. Wernicke's encephalopathy or Korsakoff's psychosis) the mortality is higher.

Treatment consists of immediate cessation of alcohol, a high caloric, high protein diet, and administration of concentrated B vitamins. In addition, general symptomatic treatment of pain with prevention of contractures and other complications is necessary. In severe cases it may take several months or even years of continued treatment before the patient is able to resume normal work.

Guillain-Barre Syndrome

This is also known as post-infectious polyradiculoneuritis. It is characterized by acute motor neuropathy with proximal and distal involvement and frequent cranial nerve paralysis. This form of PN is considered second only to alcoholic neuropathy in frequency. It affects all ages, but is more frequent in young adults.

The cause is not known but current evidence suggests an allergic basis to the illness. Pathological lesions are situated in the nerve roots and proximal portion of the peripheral nerves. These are characterized by swelling, followed by demyelination and inflammation. Approximately two-thirds of patients have history of mild respiratory or gastrointestinal infection a few days or a few weeks prior to onset. Concurrent illness, e.g. mumps or infectious mononucleosis, may be seen in some cases. Leg weakness is usually the first symptom, although paresthesias or aching pain in the calves may accompany or precede this. The weakness progresses in severity and may ascend to involve proximal leg muscles, arms, and even muscles innervated by cranial nerves. In fulminating cases, the weakness may spread to involve all extremities, bulbar and facial musculature in 24 to 72 hours after onset, reaching the peak of severity in a few days. Occasionally it may take two to three weeks to reach the maximum severity. Trunk muscles are often spared. Peripheral facial nerve involvement is seen in 85 percent of the cases.[4] In nearly half of these, facial involvement is bilateral. Bulbar muscle involvement is also common, producing dysphagia and dysarthria. Weakness of muscles in the extremities is symmetrical. In most cases distal and proximal weakness may be equal; not infrequently, proximal weakness may be more pronounced than distal. The involved muscles and nerves are tender to pressure.

Sensory involvement is often minimal. There may be paresthesias at the onset; however they usually abate by the time motor weakness is completed. Occasionally a patient may have back pain and limitation of straight-leg raising, indicating sensory root irritation. Cutaneous sensations may be minimally impaired in distal portions of the extremities. In rare cases, vibration and position sense may be markedly impaired – 'ataxic form'.

Deep tendon reflexes are always absent or markedly reduced, but the superficial reflexes are usually unchanged. Sphincter functions are not affected. Occasionally the patient may run fever and the blood pressure may fluctuate. Flushing and sweating of hands is not uncommon. Tachycardia often warrants ascent of paralytic process.

After the maximum motor disability there is a period of steady state and then recovery begins. In most patients without concurrent infection or other complications, recovery begins before the 45th day of illness. In mild cases regression begins in two to three weeks and is complete within a few weeks. In those with serious motor disability the recovery is slower, but usually complete. In some cases there is residual weakness. This is more likely to happen in those cases with respiratory failure or when the illness is prolonged. The regression of weakness in these cases is slow. It may take as long as six months or longer before substantial improvement is noted. Recurrence of Guillain-Barre syndrome is uncommon.

The prognosis for life almost totally depends on development of complications and their management.[6] Prognosis is not related to preceding illness or CSF protein level. Mortality rate with modern care is 2-19 percent. Mortality is slightly higher in adults than children. There are three common causes of death: respiratory failure, intercurrent infection and deep vein thrombosis followed by embolism.

Respiratory failure often occurs between the second and 21st day of onset; average by about the 12th day of illness. In those cases where all four extremities are involved, a careful watch for development of tachycardia or bulbar signs is necessary. When any one of these signs appears, assisted respiration should be considered. At that point the patient should be transferred to an institution where such facilities are available. If laboratory facilities for respiratory function studies are available, vital capacity and blood gases should be determined frequently. Reduction of ventilatory capacity to 30 percent or less is an indication for assisted respiration.[6] Ventilatory assistance should be continued until the vital capacity exceeds 50 percent of the predicted normal and the blood gases are reasonably adequate.

Diagnosis of Guillain-Barre syndrome is easy from clinical features of sudden onset of motor weakness and rapid progression. Cerebrospinal fluid reveals 'albuminocytological dissociation', i.e. elevation of proteins without significant change in cell count. It is important to realize that protein elevation varies from patient to patient and may be moderate – 50 to 100 mg/100 ml – or pronounced – over 200 mg percent. Cerebrospinal fluid proteins may be normal in the early stage. In one series, 39 percent of patients had protein levels less than 75 mg percent at onset of illness.[4] The peak of protein elevation is reached by the third week of illness. If the CSF proteins are normal in a suspected case at an early stage, examination should be repeated later. The CV are slow. Other laboratory abnormalities depend on any concurrent illness.

Differential diagnosis should include:

1. Poliomyelitis – fever, severe pain in the extremities, no sensory loss, elevation of cells and proteins in CSF, and asymmetrical involvement.
2. Post-diphtheric polyradiculopathy – rare in North America, often palatal and accommodation muscle paralysis at onset, throat culture for the organism.
3. Acute intermittent porphyria – diffuse pain, abdominal symptoms, mental derangement, dark urine, and normal CSF.
4. Hypokalemic periodic paralysis – often family history. Attacks short-lived, no sensory symptoms, normal CSF.

Treatment consists of good nursing care, symptomatic treatment of pain, prevention of deformities, prevention of deep vein thrombosis by passive movements, prevention of respiratory tract infection by frequent changing of position and suction, a careful watch for respiratory failure before it sets in, and assisted respiration when necessary. Because of favorable prognosis and variable course in untreated cases, the effectiveness of corticosteroids cannot be established. The use of these drugs may be justified at an early stage in severe cases, preferably within 48 to 72 hours of onset of severe motor deficit. Prednisone, 10 mg qid, is often an adequate dose. If no improvement is noted within ten days, the treatment should be discontinued. One should always be aware of possible masking of concurrent infections with steroids. There is as yet no definite proof that recovery process is more rapid or more complete on steroids than in untreated cases.

Diabetic Polyneuropathy

Peripheral nerve involvement in diabetes mellitus can be of many types: mononeuropathy, mononeuritis multiplex, painful proximal asymmetrical motor neuropathy, autonomic neuropathy and the most common form – symmetrical distal sensory neuropathy. Only this last type fits the definition of polyneuropathy.

Although a large percentage of asymptomatic diabetics have slowed peripheral nerve conduction, symptomatic patients with fully developed features of PN account for only four percent of the diabetic population.[4] This type of polyneuropathy often develops in elderly patients with mild diabetes which may have been unrecognized for many years. It is thought to be due to defective carbohydrate metabolism of myelin sheath or Schwann's cells.

Onset is gradual and a number of patients may have no discomfort even when they have gross neurological deficit. The neuropathy almost exclusively involves lower extremities, very rarely affecting upper extremities. There is numbness, coldness, or a feeling of the feet being wrapped in cotton wool. In some cases, deep aching nocturnal pain in the legs may be bothersome. This is often relieved on getting out of bed. In rare cases burning or lancinating pain may be a prominent feature and the patient may not tolerate bed clothes or shoes – 'hyperalgesic' type. Most cases have loss of all sensory modalities, though the earliest and most marked loss is seen in vibration sense. Cutaneous sensory loss may be of irregular 'stocking' distribution. Trophic changes in the skin of the lower extremities may be a feature. The involved muscles and nerves are tender to pressure. Motor weakness is usually mild, often limited to dorsiflexors of the feet and toes. Ankle jerk is always absent and knee jerk reduced in about half of the cases.

The diagnosis is based on history and glucose tolerance test. Some patients may have no discomfort, going unrecognized until complications of neuropathy develop. Realizing this problem, many endocrinologists check all their patients over the age of 60 routinely for evidence of peripheral neuropathy.

Sensory diabetic PN is usually chronic. Even though it is not related to severity of diabetes, good diabetic control will often have a useful effect on peripheral neuropathy. In some cases, initiation of diabetic control at first may worsen the symptoms of polyneuropathy, but improvement eventually results. The other measures are those for general treatment of polyneuropathy. General principles for treatment of polyneuropathy are:

1. Judicious rest of the affected part.
2. Appropriate nursing care.
3. Avoid further damage by eliminating the known cause and preventing complications.
4. Relief of pain.
5. Passive range of movements to avoid contractures and development of deep vein thrombosis.
6. Attempts towards total rehabilitation of the individual. ◀

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